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# PATHCHAT

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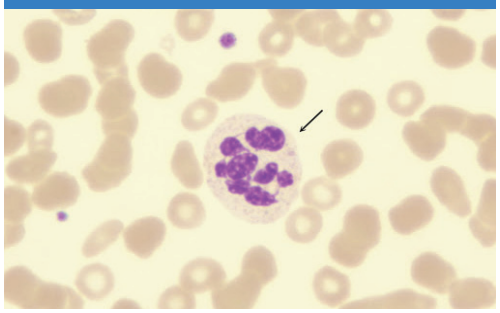
# Myelodysplastic syndromes



The myelodysplastic syndromes (MDS) are a group of clonal haematopoietic disorders characterised by progressive bone marrow failure due to ineffective haematopoiesis. There are progressive cytopenias involving one or more of the myeloid cell lines, with a variable increased risk of development of acute leukaemia.

## Epidemiology

Although MDS may occur at any age, including childhood, this condition primarily affects the elderly, with the median onset in the seventh decade of life. The incidence increases significantly with age, ranging from 0.7 per 100 000 population during the fourth decade of life, to 20.8 to 36.3 per 100 000 after the age of 70 years. At all ages, MDS is more common in males. Statistics from 1999 show that 13 000 new cases occur annually, surpassing chronic lymphocytic leukaemia as the most common form of leukaemia in the western hemisphere. MDS is found worldwide and is similar in characteristics throughout the world.

## Aetiology

MDS occurs following haematopoietic stem cell injury and, in the majority of cases, the cause is unknown. MDS may be secondary to exposure to alkylating agents, ionising radiation or both, having a latency period of five to ten years. Treatment with topoisomerase II inhibitors may predispose to acute leukaemia following a latency period of one to five years with a myelodysplastic phase in some patients. In addition, tobacco smoke, pesticides, industrial chemicals (for example, benzene) and heavy metals (lead and mercury) may be predisposing agents.

## Clinical features

Many patients with MDS are initially asymptomatic, with the condition being discovered incidentally on a routine blood count. Others have symptoms of anaemia, which is frequently macrocytic, but refractory to treatment with folate and Vitamin B12. Neutropenia, thrombocytopenia or both may be found initially or may appear later. Organomegaly is usually not a feature.

## Laboratory findings

The full blood count abnormalities vary from a macrocytic anaemia to pancytopenia and are usually of a mild to moderate degree on presentation. The peripheral smear shows

evidence of a variable degree of dysplasia affecting the red cells, granulocytes and platelets. Features include the presence of macrocytes, neutrophils that have abnormal nuclear lobularity (for example, hyposegmentation), hypogranularity and large abnormal platelets. The bone marrow is typically hypercellular and shows various morphologic abnormalities (dysplasia), which may affect a single cell line or all three lineages. In the erythroblasts, dyserthropoiesis may be present in the form of nuclear abnormalities, for example, budding, internuclear bridging, megaloblastoid changes or the presence of ring sideroblasts on iron staining.

Dysgranulopoiesis, in the form of nuclear hypolobulation (pseudo Pelger-Huët), cytoplasmic hypogranularity, hypersegmentation and dysmegakaryopoiesis in the form of micromegakaryocytes, nuclear hypolobulation or multinucleation may be present. The blast percentage in the bone marrow (and peripheral blood) is essential for subclassification and prognostication.

The World Health Organisation (WHO) classification (see Table 1) defines the different subtypes of MDS, based on the cytopenias, type and degree of dysplasia present, blast percentage, and presence or absence of Auer rods and ring sideroblasts.

**Table 1: Peripheral blood and bone marrow findings in MDS**

| Disease | Blood findings | Bone marrow findings |
|---|---|---|
| Refractory cytopenias with unilineage dysplasia (RCUD) | Unicytopenia/ bicytopenia<br>Blasts < 1% | Unilineage dysplasia<br>< 5% blasts; <15% ring sideroblasts |
| Refractory anaemia with ring sideroblasts (RARS) | Anaemia<br>No blasts | ≥ 15% ring sideroblasts<br>Erythroid dysplasia; < 5% blasts |
| Refractory cytopenia with multilineage dysplasia (RCMD) | Cytopenia(s)<br>Blasts <1%, no Auer rods<br>< 1x $10^9$/L monocytes | Dysplasia in ≥ 2 myeloid lineages<br>< 5% blasts, no Auer rods<br>+/- 15% ring sideroblasts |
| Refractory anaemia with excess blasts-1 (RAEB-1) | Cytopenia(s)<br>< 5% blasts, no Auer rods<br>< 1x $10^9$/L monocytes | Unilineage or multilineage dysplasia<br>5-9% blasts, no Auer rods |
| Refractory anaemia with excess blasts-2 (RAEB-2) | Cytopenia(s)<br>5–19% blasts, Auer rods +/-<br>< 1x $10^9$/L monocytes | Unilineage or multilineage dysplasia<br>10-19% blasts<br>Auer rods +/- |
| Myelodysplastic syndrome – unclassified (MDS-U) | Cytopenias<br>≤ 1% blasts | Dysplasia in < 10% cells in one or more myeloid cell lines; < 5% blasts<br>cytogenetic abnormality |
| MDS associated with isolated del (5q) | Anaemia<br>Normal or increased platelets<br>Blasts < 1% | Normal to increased megakaryocytes with hypolobated nuclei<br>< 5% blasts, no Auer rods<br>Isolated del (5q) cytogenetic abnormality |

Adapted from *WHO classification of tumours of haematopoietic and lymphoid tissues*, 4th edition, 2008.

## Differential diagnosis

The approach to the diagnosis of MDS should begin with the exclusion of more common types of anaemia, specifically including folate and Vitamin B12 deficiencies. Myelodysplastic changes may also be caused by certain drugs, including chemotherapeutic agents, biologic agents, heavy metal exposure, granulocyte colony stimulating factor (G-CSF) and HIV.

Bone marrow aspiration (to evaluate morphologic abnormalities of haematopoietic precursors), bone marrow biopsy (to assess marrow cellularity and topography) and cytogenetic investigation to identify non-random chromosomal abnormalities (which are observed in about 50% of MDS cases) are all mandatory for diagnosis and prognosis.

## Treatment and prognosis

The MDS subtypes (Table 1) show considerable clinical hetereogeneity, and although progression to acute myeloid leukaemia (AML) is the natural course in many cases of MDS, the percentage of patients who progress varies substantially in the various subtypes, those having increased blasts have a greater tendency to transform to AML. The course in the majority of patients is progressive bone marrow failure, with RA and RARS being indolent with a very low incidence of evolution to AML. About 50% of deaths occur as a result of bleeding or infection. The International Prognostic Scoring System (IPSS) (Table 2), based on the percentage of bone marrow blasts, cytogenetics and number and degree of cytopenias, is useful for predicting survival and risk of leukaemic transformation. It facilitates decision-making in individual cases. Leukaemia occurring as a result of MDS is notoriously resistant to treatment.

The median survival rates in the different risk groups based on the score are shown in Table 3

**Table 2: International Prognostic Scoring System (IPSS) and its prognostic significance**

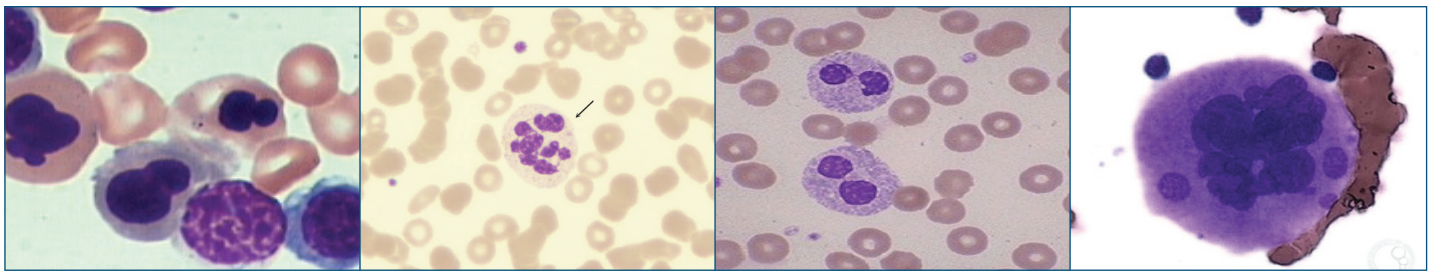
| Score | 0 | 0.5 | 1 | 1.5 | 2 |
|---|---|---|---|---|---|
| % bone marrow blasts | < 5% | 5-10% | | 11-19% | 20-30%^ |
| Karyotype* | Good | Intermediate | Poor | | |
| Cytopenias** | 0-1 | 2-3 | | | |

^ This group is defined as AML in the WHO classification

* Karyotype: Good = normal, -Y, del (5q), del (20q)
Poor = complex (≥3 abnormalities) or chromosome 7 anomalies
Intermediate = other abnormalities

**Cytopenias: Hb < 10g/dL
Neutrophils < 1.8 x $10^9$/L
Platelets <100 x $10^9$/L

Adapted from *WHO classification of tumours of haematopoietic and lymphoid tissues*, 4th edition, 2008.



Dysplastic red cell precursors | Dysplastic neutrophil | Dysplastic neutrophils (pseudo Pelger-Huët) | Dysplastic megakaryocyte

**Table 3: Median survival rates according to risk groups**

| | | | Median survival (years) | |
|---|---|---|---|---|
| **Risk groups** | **Score** | **< 60** | **>60** | **All patients** |
| Low | 0 | 11.8 | 4.8 | 5.7 |
| Intermediate I | 0.5-1 | 5.2 | 2.7 | 3.5 |
| Intermediate II | 1.5-2 | 1.8 | 1.1 | 1.2 |
| High | >2.5 | 0.3 | 0.5 | 0.4 |

Adapted from Greenberg, P et al. 1997. International scoring system for evaluating progress in MDS. *Blood*,89:2 079–88.

In lower risk patients, the aim of therapy is haematological improvement, whereas for patients with higher risk disease, limiting disease progression and improving survival are the objectives.

In the former group, supportive care with transfusion of blood and blood products is the mainstay, as well as agents such as erythropoietin and G-CSF in selected patients.

Therapeutic options for higher risk patients include allogeneic haematopoietic stem cell transplant (HSCT), high-intensity therapy, low-dose chemotherapy (for example, low-dose cytarabine) and hypomethylating agents. The newer drugs include lenalidomide, and the hypomethylating agents azacitidine and decitabine.

For these more intense therapeutic options, careful patient selection is mandatory with considerations including age, performance status, presence of co-morbid conditions and the availability of an HLA-matched donor.

## Conclusion

MDS is a not an uncommon cause of unexplained macrocytic anaemia and other cytopenias, particularly in the elderly. Diagnosis requires the examination of the peripheral blood and bone marrow, as well as cytogenetic analysis, which will allow subtyping and prognostication. There is progressive bone marrow failure, with the more severe subtypes progressing to AML. Treatment may be supportive or may include chemotherapy with or without HSCT in selected patients with high-risk disease and favourable clinical status.

## References


1. Swerdlow, SH, Campo, E, Harris, NL, et al. (Eds.). 2008. *WHO classification of tumours of haematopoietic and lymphoid tissues*. 4th ed.
2. Cazzola, MC, Malcovati, I. 2005. Myelodysplastic syndromes – Coping with ineffective haematopoiesis. *The New England Journal of Medicine*,352:536–538.
3. Greenberg, P, Cox, C, Le Beau, MM, et al. 1997. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood*, 89:2 079–2 088.
4. Louw ,VJ, Bassa, F, Chan, SW, et al. 2011. Guideline for the treatment of myelodysplastic syndromes (MDS) in South Africa. *South African Medical Journal*, 101:900–906.